ROLE OF METASTATIC LYMPH NODES TO TOTALLY REMOVED LYMPH NODES RATIO IN BREAST CANCER?

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ABSTRACT

To determine prognostic ratio of metastatic lymph nodes to totally removed lymph nodes (MLN/TRLN) on overall and progression-free survival with diagnosis of breast cancer. Radiation Oncology department of Kayseri Training and Research Hospital, relationship of MLN/TRLN between prognosis and other prognostic factors was evaluated in T1-3 and N1-3 non-metastatic breast cancer patients. Two hundred female patients and 5 male patients with an average age of 56 years were enrolled in this study. Of all patients, 63.4% of the patients were postmenopausal and modified radical mastectomy was performed in 96.6% of them. While 93.2% of the patients were diagnosed with invasive ductal carcinoma, 52.7% of them had clinical N1 disease, 62% of them were staged as T2, 94% of them received chemotherapy and 57.1% of them received hormonal therapy. Metastatic lymph node ratio below 0.2 was 48.8%, between 0.21-0.65 it was 35.1% and above 0.65% it was 16.1%. Five-year Overall survival and progression-free survival rates were 76% and 58% respectively. Statistically significant difference was found between MLN/TRLN and age ($p=0.044$), chemotherapy ($p=0.039$), pathological lymph nodes ($p<0.001$) according to Pearson's Chi-Squared test. Factor affecting overall survival was Progesterone receptor status ($p=0.021$) and for progression-free survival they were gender ($p=0.003$) and human epidermal growth factor receptor 2 ($p=0.018$). Univariate and multivariate analysis found that gender ($p=0.04$, OR 5.9, CI: 1.7-19.6) and lymph node ($p=0.05$, OR: 1.4, CI: 0.9-2.1) were significant factors affecting progression-free survival.

MLN/TRLN was shown to have no effect on prognosis in non-metastatic breast cancer patients due to small number of patients and short follow-up period.

Keywords: Breast cancer, metastatic lymph nodes, removed lymph nodes.

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INTRODUCTION

There have been many studies in the treatment of breast cancer starting from the discovery of anti-cancer drugs and radiotherapy (RT). Given that breast cancer show wide variety of biological difference, heterogeneity and consists of subgroups with different prognosis, there is still no consensus on the optimal treatment. Therefore, in order to individualize treatment, it is required to identify patients with good or poor prognosis (1,2).

While lymph node metastasis is an indicator of poor prognosis, it is still the most powerful prognostic factor for disease-free survival and overall survival. Also axillary lymph node involvement is still considered the most important sign of progressive disease. Therefore axillary lymph node dissection besides providing locoregional control, has huge contribution to accurate staging and to the decision-making process of which patient should be given adjuvant therapy (1-4). In the literature, in cases with node-negative axillary dissection, 5-year survival was reported to be 88% and 10-year survival, 65%. In cases with node-positive axillary dissection, when 4 or more axillary lymph node metastases were present, 5-year survival was reported to be 32% and 10-year survival, 13% (3).

Pathological staging after axillary dissection is gold standard to determine if chemotherapy and/or radiotherapy will be useful. Removal of numerous lymph nodes and excision of metastases provide better prognosis. In many studies, it was observed that number of metastatic lymph nodes were increased in parallel to the number of dissected lymph nodes. In some studies 10 or more dissected lymph nodes, and in some of them 16 and more dissected lymph nodes were shown to represent axillary status in a reliable manner. However, there are reports saying that removal of 4 to 6 lymph nodes with more limited dissection would be enough. Yet, the optimal number of lymph nodes and extension of axillary dissection to provide axillary control and adequate prognostic value haven't been clarified.

Radiotherapy has an important role in the breast cancer treatment. Mastectomy, large tumors, tumors with lymph node metastases and breast-conserving surgery are indications for adjuvant RT. In the treatment planning, target volume is determined by evaluation of patient, tumor, and treatment characteristics. Radiotherapy after mastectomy is often recommended for T3-4 cases with high risk of local recurrence or patients with 4 and more axillary lymph node metastasis. However, in the recent years, patients with 1 to 3 lymph node metastasis have been shown to be sensitive to radiotherapy and it has been increasingly indicated in these patients. Currently the indication for adjuvant RT and determination of RT region are decided according to the number of metastatic lymph nodes (1).

In the recent studies, ratio of metastatic lymph nodes to totally removed lymph nodes (MLR) has been reported to provide better prognostic information while grouping nodal

disease according to number of metastatic lymph nodes and making adjuvant treatment plan decisions.

In this study, relationship of MLR between prognosis and other prognostic factors was evaluated in T 1-3 and N 1-3 non-metastatic breast cancer patients. Two hundred female patients and 5 male patients with an average age of 56 years were enrolled in this study. Of all patients, 63.4% of the patients were postmenopausal and modified radical mastectomy was performed in 96.6% of them. While 93.2% of the patients were diagnosed with invasive ductal carcinoma, 52.7% of them had clinical N1 disease, 62% of them were staged as T2, 94% of them received chemotherapy and 57.1% of them received hormonal therapy. Metastatic lymph node ratio below 0.2 was 48.8%, between 0.21-0.65 it was 35.1% and above 0.65% it was 16.1%.

The median follow-up time was 20 months (range: 1-112 months). Five-year overall survival and progression-free survival rates were 76% and 58%, respectively. Twenty nine patients died due to either cancer related or other causes. In 43 patients local recurrence or distant metastasis were detected. For age ($p=0.044$), chemotherapy ($p=0.039$) and pathological lymph nodes ($p<0.001$), statistically significant results were observed with MLR according to Pearson's Chi-Squared test. Factor affecting overall survival was Progesterone receptor status ($p=0.021$) and for progression-free survival they were gender ($p=0.003$) and human epidermal growth factor receptor 2 ($p=0.018$) (Table 1). According to univariate and multivariate analysis, gender ($p=0.04$, OR 5.9, CI: 1.7-19.6) and lymph nodes ($p=0.05$, OR: 1.4, CI: 0.9-2.1) were significant factors affecting progression-free survival.

In our study, in the light of literature, the threshold for MLR was taken as 0.20. Although overall survival and progression-free survival were observed better in patients with MLR of less than 0.2 than in MLR of 0.21-0.65, and above 0.65, it wasn't statistically significant. When MLR was examined for relation to other parameters, age ($p=0.044$), chemotherapy ($p=0.039$) and pathological lymph nodes ($p<0.001$) were found to be significant. Vinh-Hung et al stated that in node-positive breast cancer patients MLR had prognostic importance and it was an alternative to pN stage (6). In the meta-analysis of Liu et al, it was reported that in breast cancer patients, MLR had prognostic significance when the threshold (cut-off) values were taken as 0.2 and 0.65(4). There are also reports using 0.25 and 0.7. These differences were mostly result of varied number of patients and treatment modalities (e.g., surgical approach, adjuvant therapy, histological type, size, grade and hormone receptor status of the tumor) (2,4,5,6). In the study of Altundag et al, they evaluated the importance of pathologic node (pN) stages and MLR classification in predicting prognosis. They analyzed N1, N2 and N3 clinical disease by dividing them into subgroups and reported that both pN stage and MLR classification were independent prognostic factors for overall survival; MLR classification was found to show prognostic distinction for overall survival more accurate and clearer thus it could give more accurate results in both staging and adjuvant

treatment planning (2). Fortin et al worked with T1-2 stage node-positive patients and suggested axillary radiotherapy to patients who had 1 to 3 lymph nodes metastasis with MLR of 0.4 and above and to patients who had 4 or more lymph node metastasis with MLR above 0.5 (5). In the study of Truong and colleagues which was published in 2005, they evaluated patients who had no radiotherapy treatment before and who had 1 to 39 lymph nodes removed. Most significant MLR threshold was found as 0.25 to predict locoregional recurrence, distant metastasis and overall survival. Radiotherapy was suggested to patients with MLR more than 0.25 after mastectomy. In 2007, in their other work, to predict locoregional recurrence, they reported that MLR was more significant than pN stage and also because 10-year locoregional recurrence risk was above 20% in patients with MLR more than 0.2, they recommended radiotherapy to these patients after mastectomy (8).

Karlsson et al found that in node-positive patients who did not receive radiotherapy, with the increase in number of non-metastatic lymph nodes, locoregional recurrence was significantly reduced and in the group of patients who had 1 to 3 positive lymph nodes and less than 10 non-metastatic lymph nodes, it was indicated that a 10-year cumulative incidence of locoregional recurrence was over 20% and these patients should receive post-mastectomy radiotherapy (9).

CONCLUSIONS

In conclusion, MLR was shown to have no effect on prognosis in non-metastatic breast cancer patients due to small number of patients and short follow-up period. These studies should be supported by more extensive researches to elucidate the role of MLR in prognosis and in adjuvant radiotherapy indication.

Table 1. Overall (OS) and progression-free survival (PFS) and p value (p<0.05)

Variable	No. of patients	Mean OS (months)	P value (<0.05)	Mean PFS (months)	P value (<0.05)
Gender			0.242		0.003
male	5	29.5 (29.1-29.7)		22.4 (14.5-30.3)	
female	201	84.4 (73.3-95.4)		78.4 (69.1-87.6)	
Age (years)			0.885		0.988
<60	128	83.5 (68.8-98.2)		77.2 (65.9-88.4)	
=>60	77	80.1 (63.8-94.7)		70.7 (53.9-87.5)	
Menopausal status			0.804		0.318
premenopausal	68	65.3 (57.1-73.5)		55.3 (46.1-64.5)	
postmenopausal	131	83.0 (69.8-96.2)		82.1 (71.2-89.6)	
unknown	6	-		30.2 (20.8-39.6)	
Performance status			0.199		0.685
ECOG 0	120	93.4 (83.9-103.0)		77.0 (64.4-89.6)	
ECOG 1	85	74.0 (72.6-94.7)		71.6 (57.7-85.5)	
Pathology			0.980		0.694
invasive ductal	191	86.2 (75.7-96.7)		78.4 (68.8-88.0)	
inflammatory	9	68.3 (51.8-84.8)		56.9 (31.1-82.7)	
the other	5	70.9 (35.9-105.8)		54.8 (19.9-98.7)	
Tumor size			0.883		0.147
I	43	86.9 (71.6-102.3)		93.3 (79.5-107.1)	
II	127	59.3 (53.1-65.6)		53.1 (46.1-60.1)	
III	35	45.6 (40.0-51.1)		40.5 (34.0-47.0)	
Lymph node status			0.275		0.079
I	108	85.2 (72.1-98.3)		78.3 (66.0-90.6)	
II	51	68.1 (59.3-76.9)		61.6 (52.7-70.5)	
III	46	34.3 (30.0-38.5)		51.1 (20.0-82.2)	
Histologic grade			0.699		0.719
I	48	94.3 (78.4-110.2)		85.8 (69.4-101.5)	
II	90	76.3 (63.6-92.1)		69.5 (57.5-81.4)	
III	53	63.8 (52.7-73.5)		60.5 (48.0-72.9)	
unknown	14	47.2 (38.9-55.4)		44.0 (34.8-53.1)	
Perinodal involvement			0.349		0.676
no	70	89.9 (73.1-106.8)		76.2 (61.2-91.3)

	yes	135	77.2 (64.8-89.6)		74.5 (63.8-85.2)	
Lymphovascular invasion	no	87	94.2 (82.7-105.7)	0.121	72.1 (57.7-87.5)	0.596
	yes	118	66.7 (72.6-94.7)		65.7 (57.7-74.7)	
ER status	positive	120	86.4 (74.8-98.0)	0.808	81.8 (70.2-93.4)	0.114
	negative	68	66.5 (58.4-74.6)		66.3 (55.6-77.1)	
	unknown	17	82.2 (72.6-94.7)		52.0 (29.6-74.5)	
PR status	positive	102	83.0 (67.5-98.6)	0.021	82.2 (70.6-93.9)	0.484
	negative	99	72.1(62.3-81.9)		59.6 (48.7-70.4)	
	unknown	4	21.6 (72.6-94.7)		26.2 (11.5-40.8)	
HER2	negative	123	88.4 (77.0-99.7)	0.761	86.2 (76.2-96.2)	0.018
	positive	65	47.1 (39.2-54.9)		39.4 (32.2-46.6)	
	unknown	17	68.6 (57.2-80.0)		68.0 (47.6-88.4)	
Number of removed lymph nodes	<16	100	81.0 (69.5-92.5)	0.423	74.2 (61.2-87.2)	0.764
	=>16	105	80.8 (72.6-94.7)		76.5 (64.4-88.6)	
MLR score	0.0-0.2	100	83.1 (70.2-96.0)	0.915	77.5 (64.9-90.0)	0.526
	0.21-0.65	72	82.1(62.9-101.39		72.9 (58.0-87.7)	
	=>0.65	33	57.4 (45.3-69.5)		57.2 (45.2-69.2)	
Surgery	mastectomy	196	83.5 (71.9-95.1)	0.273	76.2 (66.6-85.8)	0.234
	lumpectomy	9	77.5 (71.9-95.1)		75.5 (62.9-88.0)	
Chemotherapy	yes	193	86.1 (75.3-96.9)	0.307	75.8 (65.9-85.7)	0.610
	no	12	60.2 (36.7-83.7)		58.4 (30.7-86.3)	
Hormonotherapy	yes	117	86.0 (71.8-100.1)	0.450	72.2 (60.3-84.1)	0.204
	no	88	64.4 (55.3-73.5)		66.6 (57.8-75.3)	

ABBREVIATIONS

ECOG: Eastern Cooperative Oncology Group;
MLR: metastatic lymph nodes to totally removed lymph nodes ratio;
N : lymph node;
OS : overall survival;
PFS : progression-free survival;
T : tumor size.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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